Proposed Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 3-9, 11-20, 23, 24, and 40-50 are pending in the application, with claim 40 and 50 being the only independent claims. Claims 1, 2, 10, 21, 22, and 25-39 have been previously canceled without prejudice to or disclaimer of the subject matter therein, with claims 25-39 being drawn to non-elected invention. New claims 49 and 50 has been added. Support for the amendment to claim 13 is found, for example, in the published application at paragraphs [0097] to [0099] and in Figure 6. Support for the amendment to claim 40 is found, for example, in the published application at paragraphs [0051], [0072], [0089] to [0114], and the Examples. Support for new claim 49 is found, for example, in the published application at paragraph [0132]. Support for new claim 50 is found, for example, in the published application at paragraphs [0003], [0050] to [0060], [0072], [0089] to [0094], and [0172], in original claims 1, 10 and 11, and in Figure 6. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Examiner Interview of February 1, 2010

Applicants thank Examiner Maria B. Marvich for the courtesy of a telephone interview held with Applicants' representatives, John Covert and Anbar F. Khal, on February 1, 2010, regarding the present application. During that interview, the claim

rejections under 35 U.S.C. § 112, first and second paragraphs, were discussed, and Applicants' representatives pointed out differences between the invention and the applied references. With regard to the rejection of claim 40 under 35 U.S.C. § 112, first and second paragraphs, for the language, "homogenously mixed as a result of flowing through the filling elements in the lysis reactor so that irreversible denaturation of the biomolecule of interest is avoided and the cultivated host cells are disintegrated by alkaline lysis in the absence of shear forces," possible amendments were discussed to address the Examiner's concerns with this language. In particular, the Examiner suggested amending the claim to recite the conditions of homogenously mixing and absence of shear forces in an active tense, and removing the language directed to avoiding irreversible denaturation of the biomolecule of interest. With regard to the rejection of claim 40 under 35 U.S.C. § 112, second paragraph, for the language of method step c) of "transporting" the lysed cell solution via the neutralization reactor, Applicants' representatives explained that step c) is directed to neutralizing the lysed cell solution and that the term "transporting" is not meant to require a particular type of movement or manipulation, as asserted by the Examiner. Applicants' suggested changing the term "transporting" to "neutralizing", and the Examiner indicated that this change should be acceptable.

The above amendment and following remarks incorporate the suggestions discussed with the Examiner during the interview to overcome the claim rejections. Entry of the above amendments and allowance of the present application is respectfully requested.

Claim Objections

Claim 40 has been objected to because the Examiner states that the preamble recites "a host cell" whereas later claim language refers to "host cells", and the reference to cells should be either in singular or plural to ensure proper anteeedent basis. Applicants respectfully disagree with the Examiner's position. Applicants respeetfully submit that the recitation "a host cell" in the preamble is introductory and not the antecedent for the recitation of host cells in the body of the claim. Thus, in the body of present claim 40, step a) recites "providing a cell suspension of *host cells* that have been cultivated to produce a biomolecule of interest." *See also* MPEP 2173.05(e) ("The mere fact that the body of a claim recites additional elements which do not appear in the claim's preamble does not render the claim indefinite under 35 U.S.C. 112, second paragraph."). However, to expedite prosecution, and without acquieseing to the objection, Applicants have amended claim 40, line 2, to recite "host cells," as suggested by the Examiner. Applicants therefore respectfully request that this objection of claim 40 be withdrawn.

Claim 40 has also been objected to because the Examiner asserts that the claim mentions introducing or transporting of solution into the reactors but does not mention how the solutions are introduced or transported. The Examiner asserts that the claim should be further amended in the preamble to recite "wherein transportation between the reactors is mediated by pressure or pumps." See Office Action, page 2. Applieants respectfully disagree. Applicants submit that the claim does not require a recitation of a particular means for achieving introduction or transportation of solutions in order to be sufficiently clear. It is sufficient to state, as recited in present claim 40, that the reactors

are fluidly connected and there are flows of the solutions into or via the reactors. Further, the specification does not disclose such particular means (e.g., pressure or pumps) to be essential to the invention. *See* MPEP 2172.01. Rather, the specification provides pressure or pumps as a *preferred* manner of transportation. *See, e.g.,* paragraphs [0091] and [0099] of the published application. *See also* MPEP 2164.08(c) ("In determining whether an unclaimed feature is critical, the entire disclosure must be considered. Features which are merely preferred are not to be considered critical. *In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976)."). Applicants therefore respectfully request that this objection of claim 40 be withdrawn.

Claim 8 was objected to because the Examiner alleges that the method of claim 8 reciting pressurized air is in addition to the method of claim 48 reciting pressurized gas. Applicants respectfully submit that the pressurized air of claim 8 further describes the pressurized gas of claim 48, since "air" is one example or species of a gas. To expedite prosecution, and without acquiescing to the objection, Applicants have amended claim 8 to clarify that the applied pressurized gas is pressurized air. Applicants believe appropriate correction has been made, and respectfully request that the objection of claim 8 be withdrawn.

Claim 18 was objected to because the Examiner states that the language "a concentration step" and "a condition step" should read "the concentration step" and "the condition step." Claim 18 has been amended to incorporate the Examiner's suggestion. Applicants believe appropriate correction has been made, and respectfully request that the objection of claim 18 be withdrawn.

Claim 23 was objected to because the Examiner alleges that the language "step a) is operated in a continuous mode" is not clear. In particular, the Examiner asserts that step a) comprises several parts and it is not clear which part is operated continuously. Office action, page 3. Applicants respectfully disagree. Independent claim 40 clearly recites a step of "a) providing a cell suspension of host cells . . .". Thus, the step a) is a step of "providing a cell suspension." Claim 23 recites that "step a) is operated in a continuous mode." It is therefore clear that the step of "providing a cell suspension" is operated continuously. The other features recited in step a) further describe the cell suspension that is being provided in a continuous mode. Applicants therefore respectfully request that this objection of claim 23 be withdrawn.

Claim 24 was objected to because the Examiner alleges that it is unclear from the language of the claim as to when the cell suspension is cryo-pelleted. To expedite prosecution, and without acquiescing to the objection, Applicants have amended claim 24 to recite "the cell suspension provided in step a) is obtained from a cryo-pelleted cell suspension." Applicants believe appropriate correction has been made, and respectfully request that this objection of claim 24 be withdrawn.

Rejections under 35 U.S.C. § 112

Rejections under 35 U.S.C. § 112, second paragraph

Claim 40 was rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 40 was rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential steps, such omission

amounting to a gap between the steps. The Examiner alleges **(1)** that the omitted steps are how the cell suspension and lysis solution are "homogenously mixed as a result of flowing through the filling elements in the lysis reactor so that irreversible denaturation of the biomolecule of interest is avoided and the cultivated host cells are disintegrated by alkaline lysis in the absence of shear forces," and **(2)** that the claims do not indicate how the suspension is introduced and transported, and alleges that "in order for the suspension to move there has to be some kind of force or power." Office Action, page 4. Applicants respectfully traverse these rejections.

With respect to rejection ground **(1)**, the Examiner states, "The claims appear to suggest that these effects are the result of flowing through the filling elements. If this is the case, this presents issues of new matter discussed below. If this is not the case, there appear to be critical elements and steps that are lacking in the claims." In particular, the Examiner asserts that claim 40 "requires three events in the lysis reactor 1) homogenous mixing of the suspension with lysis solution 2) avoidance of irreversible denaturation of the biomolecule and 3) disintegration of the host cells by alkaline lysis without shear force." Office Action, page 4.

With respect to event 1), the Examiner states that the specification appears to be directed to steps to ensure homogenous mixing, and cites to paragraph [0097] of the published application, which is directed to homogenous mixing of lysed cell solution in the neutralization reactor. The Examiner further alleges that it is not clear what exact steps are made to avoid the problems with the inability to generate homogenous mixing using the methods found in the art. With respect to event 2), the Examiner alleges that there appears to be mechanical or technical means of controlling degradation, and cites

paragraph [0094] of the published application. Paragraph [0094] provides parameters that can be optimized to guarantee homogenous mixing and avoid denaturation. Office Action, page 6. With respect to event 3), the Examiner cites the prior methods discussed in the Background section of the application as requiring specific steps to achieve disintegration without shear forces (at paragraph [0019]) and methods to be avoided to avoid shear forces (at paragraph [0031]), and further cites to methods in the specification directed to avoiding shear forces in the neutralization, clarification or optional conditioning steps. *See* Office Action, page 6. The Examiner alleges that the claims recite "desired outcomes without indicating how these steps are achieved." Office Action page 6.

Applicants respectfully traverse. Essential steps have not been omitted, and not new matter has been added. Present claim 40 is directed to a *method* of purifying a biomolecule of interest from host cells, the method including the *step b)* of introducing a flow of the cell suspension and a flow of a lysis solution into a lysis reactor which contains filling elements. *See, e.g.,* paragraphs [0051] and [0089] of the published application. Events 1, 2 and 3 describe conditions of conducting the method step b). The Applicants have found that events 1, 2 and 3 can be achieved by gentle flow of the cell suspension and the lysis solution through a lysis reactor that contains filling elements. Thus, the flow of the cell suspension and the flow of the lysis solution into and through the lysis reactor provides homogenous mixing of the flows in the absence of shear forces. Homogenous mixing avoids irreversible denaturation of the biomolecule of interest. *See, e.g.,* paragraph [0089] of the published application. One skilled in the art would know how to construct and operate the lysis reactor of the claimed method to

achieve these conditions. However, taking into consideration the Examiner's suggestions during the Interview, to expedite prosecution, and without acquiescing to the rejection, Applicants have amended claim 40 to recite, "introducing a flow of the cell suspension and a flow of a lysis solution into the lysis reactor into the lysis reactor, the lysis reactor containing filling elements made of glass, plastic, stainless steel or fibrous material, such that the flow of the cell suspension and the flow of the lysis solution into and through the lysis reactor provides homogenous mixing of the flows in the absence of shear forces and whereby the cultivated host cells are substantially disintegrated by alkaline lysis to produce a lysed cell solution."

The paragraphs of the application cited by Examiner as allegedly suggesting specific steps to achieve homogenous mixing without shear forces provides guidance to one of skill in the art of exemplary parameters, materials, and designs that *can be* used, adjusted and optimized in carrying out the method step b) in which the flows through the lysis reactor are homogenously mixed without causing shear forces to the biomolecule of interest. Just as one skilled in the art knows how to design, for example, static mixers to ensure a contact time of the cells with the lysis solution by optimizing mixer dimensions and flux (see paragraph [0029] of the published application), Applicants respectfully submit that one of skilled in the art would know how to optimize mechanical or technical aspects of the lysis reactor, filling elements, and the flow rates through the filling elements to have homogenous mixing without causing shear forces to the biomolecule of interest. *See, e.g.,* paragraph [0094] and Examples 2, 3, 4 and 6 of the published application. Accordingly, no essential steps have been omitted. Examples *See also* MPEP 2164.08(c), reproduced below.

Applicants therefore respectfully request that this rejection of claim 40 be withdrawn.

With respect to rejection ground **(2)**, as discussed above, Applicants submit that the claim does not require a recitation of a particular means for achieving introduction or transportation of solutions in order to be sufficiently clear to one of ordinary skill in the art. It is sufficient to state, as recited in present claim 40, that the reactors are fluidly connected and there are flows of the solutions into or via the reactors. Further, the specification does not disclose such particular means (e.g., pressure or pumps) to be critical to the invention. *See* MPEP 2164.08(c), which states:

> In determining whether an unclaimed feature is critical, the entire disclosure must be considered. **Features which are merely preferred are not to be considered critical.** *In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976).
>
> Limiting an applicant to the preferred materials in the absence of limiting prior art would not serve the constitutional purpose of promoting the progress in the useful arts. Therefore, an enablement rejection based on the grounds that a disclosed critical limitation is missing from a claim should be made **only when the language of the specification makes it clear that the limitation is critical** for the invention to function as intended. **Broad language in the disclosure, including the abstract, omitting an allegedly critical feature, tends to rebut the argument of criticality**.
> (emphasis added).

Rather, the specification provides pressure or pumps as a *preferred* manner of transportation. *See, e.g.,* paragraph [0099] of the published specification. Moreover, the term "transporting" in step c) of the claimed method is not meant to require a particular type of movement or manipulation of the lysed cell solution, as asserted by the Examiner. Indeed, in one embodiment, as recited in present dependent claim 13, the

neutralization reactor can include a tubing system fluidly connecting the lysis reactor to the clarification reactor, in which the lysed cell solution and the neutralization solution are mixed to produce the mixture comprising the lysate and the precipitate during transportation through the tubing system between the lysis reactor and the clarification reactor. However, to expedite prosecution, and without acquiescing to the rejection, Applicants have amended step c) of claim 40 to recite "c) neutralizing the lysed cell solution via the neutralization reactor...", in accordance with the discussion with Examiner during the Interview.

Applicants believe appropriate correction has been made. Applicants therefore request that this rejection of claim 40 be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

Claim 40 was rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. The Examiner alleges that the following feature of claim 40 is new matter: "homogenously mixed as a result of flowing through the filling elements in the lysis reactor so that irreversible denaturation of the biomolecule of interest is avoided and the cultivated host cells are disintegrated by alkaline lysis in the absence of shear forces." Applicants respectfully traverse this rejection.

The Examiner alleges that "Applicant has not indicated where support for this limitation is found." Applicants respectfully submit that (as noted at page 10 of the Reply to the previous Office Action, filed June 16, 2009) support can be found, for example, in the specification at paragraphs [0076] and [0080], which corresponds to

paragraphs [0089] and [0093] of the published application. Support can also be found, for example, in original claim 11, as well as in paragraphs [0051] and [0172] (Example 3) of the published application.

However, taking into consideration the Examiner's suggestions during the Interview, to expedite prosecution, and without acquiescing to the rejection, Applicants have amended claim 40 to recite introducing a cell suspension and a lysis solution into a lysis reactor containing filling elements "such that the flow of the cell suspension and the flow of the lysis solution into and through the lysis reactor provides homogenous mixing of the flows in the absence of shear forces and whereby the cultivated host cells are substantially disintegrated by alkaline lysis to produce a lysed cell solution." The specification fully supports this amendment to claim 40. For example, paragraph [0089] of the published application states:

> Preferably, the cell suspension and the alkaline lysis solution are combined, without further mixing, before entering the lysis reactor, thus forming a single flow that is **thoroughly mixed when flowing through the particulate material in the lysis reactor and achieving very gentle lysis. By avoiding disadvantageous shear forces**, plasmid DNA quality is maintained at a very high level. Furthermore, the yield of supercoiled plasmid DNA is higher as compared to conventional methods. This is due to two reasons: Firstly, degradation, which can occur when using harsher mixing conditions and devices, is reduced. Secondly, **due to the homogenous mixing, the cells are completely disintegrated** (releasing the whole pDNA-amount), avoiding local pH-extremes, which may also result in degradation of the target plasmid DNA molecule.
> (emphasis added)

Also, Example 3, paragraph [0172] of the published application states: "[T]he resuspended cells came into contact with the lysis solution (0.2 M NaOH, 1% SDS) at the first meeting point. The resulting stream was subsequently **mixed homogenously**

and contacted (1.5-2 min) in the lysis reactor **by passing the glass beads**." (emphasis added). Thus, the cell suspension and the alkaline lysis solution are homogenously mixed when flowing through in the lysis reactor containing the filling elements, which mixing is conducted in a manner that achieves very gentle lysis (host cells are disintegrated and shear forces are absent).

Applicants believe appropriate correction has been made. Applicants therefore respectfully request that this rejection of claim 40 be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 3-5, 7-9, 17-20, 23, 40, 42, 43, 47 and 48 were rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by U.S. Patent No. 6,893,879 to Petersen et al. ("Petersen").

The Examiner asserts that Petersen discloses purification of biomolecules from samples such as E. coli, and the "sample is thus inherently isolated from fermentation broth as the cells are grown in such media." The Examiner further asserts that that Petersen discloses introduction of samples into a lysis chamber that can include filling elements such as glass beads. Office Action, page 8. Applicants respectfully traverse this rejection.

Claim 40 recites "providing a cell suspension of host cells that have been cultivated to produce a biomolecule of interest, wherein the cell suspension is a fermentation broth within which the host cells were cultivated or a re-suspension of the cultivated host cells that were harvested from the fermentation broth." Petersen does not disclose the processing of a cell suspension as claimed. Petersen is directed to

processing a fluid sample for detection and/or analysis of chemical components in the sample. *See* col. 4, lns. 55-59 of Petersen. Applicants respectfully disagree with the Examiner assertion that the sample of Petersen is "inherently isolated from fermentation broth as the cells are grown in such media." There is no disclosure in Petersen of *cultivation* of cells. Petersen is concerned with the presence of analytes in samples, e.g., E. coli and salmonella in food, or bacteria in drinking water. *See* col. 4, lns. 55-59 of Petersen. The mere presence of analytes in a sample is does not suggest that the analytes were purposefully grown by being *cultivated* in a fermentation broth.

Moreover, claim 40 recites that the method "is operated on a manufacturing scale." The method of the present invention allows fast processing of large volumes, and can be used for the production of preclinical and clinical material as well as for market supply of a registered product. *See, e.g.,* paragraphs [0156] and [0157] of the published application. As described in the specification, the method may be operated to process more than 100 grams wet cells, and yielding amounts from 0.1 g to several 100 g to kg of the biomolecule of interest, which meet the demands for clinical trials as well as for market supply (see also new claim 49). *See* paragraph [0132] of the published application. *See also* paragraph [0167] of the published application. In contrast, Petersen discloses the capability of processing of fluid samples of 0.1 to 10 ml, which are magnitudes smaller than any "sample" constituting 100 grams wet cells. *See* col. 5, ln. 5 of Petersen. The cartridge of Petersen does not have the capacity to purify biomolecules on a manufacturing scale, and there is no disclosure in Petersen that suggests that the cartridge of Petersen can be successfully scaled to be used as such.

Importantly, Peterson fails to disclose introducing a cell suspension and a lysis solution into a lysis reactor containing filling elements such that the flow of the cell suspension and the flow of the lysis solution into and through the lysis reactor provides *homogenous mixing* of the flows *in the absence of shear forces*, as recited independent claim 40. Petersen describes lysing of cells mechanically or chemically to the cells captured on the beads in the lysis chamber, by vibrating the cells with ultrasonic energy or by applying a lysing reagent, respectively. *See e.g.,* col. 3, lns 32-44, col. 5, lns 37-45, col. 16 lns. 12-25, and col. 33, lns 15-28 of Petersen. Thus, Petersen clearly describes the use of beads, a filter, or other solid phase for *capturing the cells of the sample*. *See* col. 33, lns 15-28 of Petersen. *See also* col. 8, lns. 51-55 of Petersen ("The fluid sample and lysing reagent continue to flow into the lysing chamber 119 where the sample contacts a filter and the [cells] are captured. The lysing reagent continues to lyse the captured sample components."). Petersen does not disclose homogenously mixing of the cell sample with the lysing reagent when flowing through the lysing chamber. Rather, since the cells of the sample are captured in the lysing chamber, the cells do not flow through the lysing chamber and therefore can not homogenously mix with the lysing reagent flowing into and through the lysis reactor, as claimed.

For at least the foregoing reasons, independent claim 40, and claims 3-5, 7-9, 17-20, 23, 42, 43, 47 and 48, and new claim 49, which depend from claim 40, are patentable over Peterson. Applicants respectfully request the rejections be withdrawn and the claims allowed.

In addition, with respect to dependent claim 4, the Examiner asserts that Petersen discloses a clarification chamber that uses a retention layer that can comprise a

particulate matter such as beads. Office Action, page 8. Independent claim 40 recites "the clarification reactor contains a retention layer that functions to retain the precipitate but allow the lysate to flow from the clarification reactor." Dependent claim 4 recites that the particulate material of the retention layer consists of glass beads. Petersen discloses solid supports such as beads for nucleic acid *binding* so that contaminating salts can be washed waay from the sample prior to further processing. *See* col. 16, lns. 55-64 of Petersen. Petersen does not disclose the use of beads that retain the precipitate but allow the lysate to flow from the clarification reactor. For at least the foregoing reasons, claim 4 is patentable over Peterson, and Applicants respectfully request the rejection of be withdrawn and the claim allowed.

Rejections under 35 U.S.C. § 103

Rejections based on Petersen and Nochumson

Claims 3-5, 7-9, 11-20, 23, 40, 41-43 and 46-48 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Petersen in view of U.S. Publication No. 2006/0106208 to Nochumson et al. ("Nochumson"). The Examiner alleges that Petersen does not establish how the sample and lysis buffer are introduced, but asserts that Nochumson discloses that the lysis solution and cells can either be combined without further mixing prior to entering the lysis reactor or else can be introduced in the lysis reactor. *See* Office Action, pages 9 and 10. The Examiner also asserts that Nochumson discloses that flowing lysate and neutralization solution through an inline static mixer in a continuous mode. Office Action, page 10. Applicants assume that the Examiner's rejections refer specifically to one or more of dependent claims 11-16. Nochumson does not cure the deficiencies of Peterson discussed above with respect to independent claim

40. For example, Nochumson does not disclose homogenously mixing of the cell suspension and lysis solution when flowing through filling elements in the lysis reactor. Indeed, the process of Nochumson lacks a lysis reactor that contains filling elements, as claimed.

In addition, with regard to present dependent claim 13, neither Peterson nor Nochumson disclose the claimed neutralization reactor, which includes a T-type or Y-type connector and a tubing system in the form of a coil wherein lysed cell solution and the neutralization solution are combined through the T-type or Y-type connector, thus forming a single flow in which the lysed cell solution and the neutralization solution are mixed to produce the mixture comprising the lysate and the precipitate during transportation of the mixture between the lysis reactor and the clarification reactor, wherein the tubing system is configured to avoid shearing of flocks of the precipitate. Rather, as noted by the Examiner, Nochumson discloses flowing lysate and neutralization solution through an inline static mixer. Peterson is silent with regard to the manner of conducting neutralization.

For at least the foregoing reasons, independent claim 40, and claims 3-5, 7-9, 11-20, 23, 41-43 and 46-48 which depend there from, are patentable over Peterson and Nochumson. Applicants respectfully request the rejections be withdrawn and the claims allowed.

Rejections based on Petersen, Craig and Marquet

Claims 3-5, 7-9, 11, 17-20, 23, 40, 42, 43, 47 and 48 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Petersen in view of U.S. Patent No. 6,381,967 to

Craig ("Craig"). The Examiner asserts that Petersen does not disclose cryo-pelleted samples but alleges that Craig discloses this feature. Applicants assume that the Examiner's rejection refers specifically to dependent claim 24. Claims 3-9, 17-20, 23, 40, 42, 43, 47 and 48 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Petersen in view of U.S. Patent No. 5,561,064 to Marquet *et al.* ("Marquet"). The Examiner asserts the Peterson does not disclose filtrations that use filter plates but alleges that Marquet discloses this feature. Applicants assume that the Examiner's rejection refers specifically to dependent claim 6.

Applicants respectfully traverse these rejections. Craig and Marquet do not cure the deficiencies of Petersen discussed above with respect to independent claim 40. Craig and Marquet do not disclose a lysis reactor that contains sinter plates or glass beads, or other filling elements. As discussed above, Petersen discloses filling elements *for capturing* cells and applying ultrasonic energy or a lysing reagent to the captured cells. Consequently, Petersen, Craig and Marquet, alone or in combination, do not disclose or suggest that the cell suspension and the lysis solution are introduced into a lysis reactor containing filling elements such that "the flow of the cell suspension and the flow of the lysis solution into and through the lysis reactor provides *homogenous mixing* of the flows *in the absence of shear forces*," as recited independent claim 40.

For at least the foregoing reasons, independent claim 40, and claims 3-5, 7-9, 11, 17-20, 23, 42, 43, 47 and 48 which depend there from, are patentable over Peterson, Craig and Marquet. Applicants respectfully request the rejections be withdrawn and the claims allowed.

Rejections based on Petersen and Laugharn

Claims 3-5, 7-9, 17-20, 23, 40 and 42-48 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Petersen in view of U.S. Patent No. 6,274,726 to Laugharn *et al.* ("Laugharn"). The Examiner asserts the Peterson does not disclose beads that are uniform and are about 1-100 mm but alleges that Laugharn discloses this features, and that it would have been obvious to uses the lysis methods of Laugharn in the methods of Petersen. Applicants assume that the Examiner's rejection refers specifically to dependent claim 44. Applicants respectfully traverse this rejection.

Laugharn does not cure the deficiencies of Petersen discussed above with respect to independent claim 40. Moreover, a skilled artisan would not have used beads of 1-100 mm in the method of Petersen. Petersen does not disclose a method of purifying biomolecules on a manufacturing scale as claimed. Rather, Peterson discloses small-scale cartridges for processing a fluid sample for detection and/or analysis of chemical components in the sample. For example, Peterson discloses that the cartridge employs a microfabricated chip as a flow-through component for capturing a desired analyte and that the interactive regions of the cartridge have dimensions from microns to millimeters. *See* col. 4, ln. 55 to col. 5, ln. 7, col.5, lns 47-57, and col. 13, lns. 7-15 of Petersen. Moreover, Laugharn discloses the beads are used in mechanical lysis by vortexing the cell solution with the beads. *See* col. 28, lns.47-48 of Laugharn. Consequently, one would not have been motivated to use beads of the size of about 1-100 mm in the cartridge of Petersen, as the beads would have been too large to successfully incorporate into the cartridge as either a solid support or for vortexing the sample.

Moreover, even assuming, *arguendo*, there exits a motivation to combine the beads of Laugharn in the cartridge of Peterson, such combination would not have arrived at a method in which the cell suspension and the lysis solution are introduced into a lysis reactor containing filling elements such that the flow of the cell suspension and the flow of the lysis solution into and through the lysis reactor provides homogenous mixing of the flows in the absence of shear forces. The beads of Laugharn are used to mechanically lyse the cells by vortexing, which will shear the DNA present in the cells. Further, as discussed above, Peterson clearly describes the use of beads for *capturing the cells of the sample*, not for allowing the cells to flow *through* the lysis reactor containing beads and homogenously mix with the lysis solution.

Establishment of a *prima facie* case of obviousness requires that the Examiner factually show that the references in combination disclose *all* of the elements of the claims in their *proper function*, as well as provide a reasoned articulation that the combination of elements would have been known to produce a predictable result. In the present case, this burden has not been met. Applicants respectfully submit that the differences between the cited references are so great that a skilled artisan would not have been motivated to combine Laugharn with Peterson to produce the claimed invention. For at least the foregoing reasons, independent claim 40, and claims 3-5, 7-9, 17-20, 23 and 42-48 which depend there from, are patentable over Peterson and Laugharn. Applicants respectfully request the rejections be withdrawn and the claims allowed.

New Claim 50

New independent claim 50 recites a method of continuously purifying a biomolecule of interest from host cells, including a step of "simultaneously flowing the cell suspension and the lysis solution through the lysis reactor such that the cell suspension and the lysis solution homogenously mix when flowing through the filling elements in the lysis reactor without causing shear forces to the biomolecule of interest, wherein the cultivated host cells are substantially disintegrated by alkaline lysis in the lysis reactor to produce a lysed cell solution." The method is continuously operated on a manufacturing scale. Petersen does not disclose the cell suspension and the lysis solution homogenously mix when flowing through the filling elements in the lysis reactor. As discussed above with respect to independent claim 40, Peterson clearly describes the use of beads for capturing the cells of the sample. The cells do not flow through the beads and homogeneously mix with the lysis solution. Moreover, the cartridge of Petersen does not have the capacity to purify biomolecules on a manufacturing scale, and there is no disclosure in Petersen that suggests that the cartridge of Petersen can be successfully scaled to be used as such. The other cited references of Nochumson, Craig, Marquet, and Laugharn do not cure these deficiencies of Petersen. Applicants therefore respectfully request new claim 50 be allowed.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be

withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Anbar F. Khal
Attorney for Applicants
Registration No. 59,088

Date: March 4, 2010

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600
1057145_1.DOC